BIRTHWEIGHT, RAPID GROWTH, CANCER, AND LONGEVITY: A REVIEW

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The fetal growth restriction hypothesis states that retarded growth in utero promotes health problems later in life. While most of the studies on intrauterine growth retardation (as measured by birthweight) confirm this hypothesis, many researchers have found flaws in these studies. In addition, many studies have found either no correlation or a positive relation between birthweight (BW) and adult blood pressure or mortality. Furthermore, high BW leads to greater adult obesity and chronic disease, and increasing macrosomia in newborns raises the risk for birth-related problems. Increased cancer risk is also tied to higher BW, and catch-up or accelerated growth generally has negative health effects. Adult height has been found to correlate with greater BW and birthlength (BL), and several studies have found an inverse relation between height and longevity. Paradoxical findings, such as lower BW and low levels of cardiovascular disease in the developing world, are presented. Within 25 years, genetic engineering will allow in utero alterations to the fetus, resulting in higher BW and taller adults. The authors suggest that increased BW leading to larger adult body size has dangerous implications in terms of human health and survival. (*J Natl Med Assoc.* 2003;95:1170–1183.)

Key words: birthweight ♦ growth rate ♦ obesity ♦ height ♦ longevity ♦ Barker Hypothesis ♦ chronic disease

BACKGROUND

The fetal growth restriction hypothesis states that retarded growth in utero leads to health problems in later life, such as higher blood pressure (BP), type-2 diabetes, cardiovascular disease (CVD), and respiratory problems.[1] In addition, low birthweight (BW) has been used as an index of growth restriction, poor nutrition, maternal smoking, lower socioeconomic status (SES), small parental size, and preterm delivery.

While proper nutrition and healthcare are strong factors in producing healthy infants, higher BW for good health has serious consequences, because it generally produces adults with higher body weight or body mass index (BMI=kg/m^2).[2] Higher BW may result in lower perinatal mortality, but it may also increase adult health problems and mortality by promoting obesity.

The fetal growth restriction hypothesis has been challenged by many researchers. Metges[3] recently reported that the role of fetal nutrition and growth retardation on health has been met with much skepticism. Joseph,[4] Kramer,[5] Paneth, and Susser[6] found inconsistencies and conflicts within many studies and reported that proponents of this hypothesis have failed to explain temporal and international trends in coronary heart disease (CHD).

This paper reviews some of the highlights of the controversy and presents a different viewpoint on BW and childhood growth. We found over 175 papers that contradict or do not support the fetal growth restriction hypothesis. Eighty-two are presented here.

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Relationship of BW to Later BMI or Obesity

Pietilainen et al.[2] reported a positive correlation between BW and overweight or obesity in children, adolescents, and adults. High-BW infants of average length are especially vulnerable to future overweight but small infants are likely to be shorter and lighter as adults. An earlier study by Rasmussen et al.[7] also found that high BW with normal or high birthlength (BL) were risk factors for overweight and severe overweight in a population of 165,109 males.

In a study of 33,413 subjects, Seidman et al.[8] found a strong correlation between BW and overweight in late adolescence, independent of other factors. The odds ratio (OR) of being an overweight male increased from 0.81 for a BW of 2,500–2,999 g to 2.16 for a BW ≥4500 g. In females, a BW of <2,500 g had an OR of 0.83 versus 2.95 for ≥4500 g.

Supporting Evidence for the Fetal Growth Restriction Hypothesis

Huxley et al.[9] reviewed 80 studies relating BP and BW and concluded that the evidence favored the growth restriction hypothesis after adjustments were made for current weight or BMI. Smaller head circumference and accelerated postnatal growth were also related to high BP. An inverse relation between BW and systolic BP was found in 102 tests after adjustment for current weight or BMI. However, 35 tests indicated no relation or a positive relation between BW and systolic BP. Eriksson et al.[10] found low BW and Ponderal Index (kg/m^3) resulted in increased adult CHD. This study of 4,630 men also found low weight gain in the first year of life was related to higher incidence of CHD.

Animal studies have also found that poor nutrition in utero or in infancy can produce lifetime effects on growth, metabolism, diabetes, hypertension, neurodevelopment, atherosclerosis, and obesity.[11]

Problems With the Fetal Growth Restriction Hypothesis

Paneth and Susser,[6] and Lucas et al.[11] have criticized studies relating low BW to health risks in adulthood, because most of these studies adjusted for current weight and BMI. They argue that current BMI is a better indicator of increased plasma insulin levels than BW. In addition, controlling for current weight or BMI cancels the positive effect of BW via higher adult BMI on BP and the risk of glucose intolerance. Paneth, Susser, and others concluded that this adjustment allows the effect of higher BW to move towards the favored outcome of the researchers. Paneth[6], Bergel,[12] and Kramer[5] also emphasized the importance of adjusting for SES, since fetal growth is positively correlated with social status, which is also related to lower mortality.

A number of paradoxes exist that involve smaller babies having lower adult rates of CHD and diabetes. For example, the Chinese and Japanese have smaller babies than northern Europeans but have much less diabetes and CHD mortality. Since World War II, the rising BW in Scotland, Finland, and Norway has paralleled an increase in CHD.[4] In addition, sharp rises in type-2 diabetes have occurred in recent decades when "improved fetal nutrition" and increased BW should have reduced the incidence of this disease.

Another paradox is that before World War I, CHD and other chronic diseases were quite rare in the west, though most people were poor, lacked quality medical care, and were smaller. Although low BW is related to poverty, low maternal height and weight, and malnutrition, these conditions did not lead to high adult CHD and diabetes as would be predicted by the fetal growth restriction hypothesis.

Nonsupportive or Conflicting Studies

The following summarizes some of our findings that contradict or do not support the thesis that greater BW, BL, and adult body size are superior to smaller BW and adult size.

Ramifications of BW and Adolescence Body Size on BP

A number of studies have found that BW is essentially unrelated to BP in childhood and young adulthood. However, these studies also found BP strongly related to height, weight, and BMI during childhood, adolescence, and young adulthood. At greater ages, however, many factors affect BP in middle and later years. These include illness, diet, smoking, SES, alcohol consumption, stress, and the amount of overweight.

Based on >43,000 subjects, two studies from Israel found that BP is positively related to BW at 17 years of age. In addition, current weight and BMI at this age were also tied to higher BP.[13,14] A more recent study[12] found that current BMI, height, and mother's BP were positively correlated with BP in children, and low BW increased the risk for high BP only in overweight children. A Hungarian study also found that full-term children with a BW below the 10th percentile had lower rates of hypertension and dyslipidemia, compared to normal-BW children.[15]

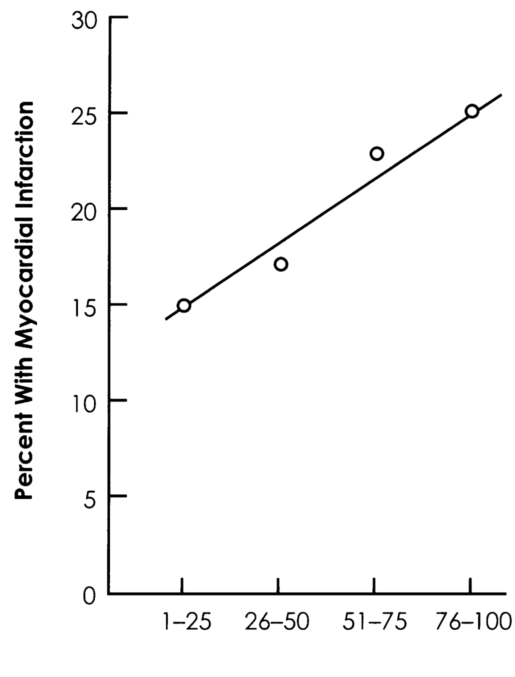
An Italian study found a relatively strong positive correlation (r=0.26) between BW and systolic BP for 1,310 adolescents.[16] This finding is supported by Williams and Poulton,[17] who evaluated the BP of over 800 twins and singletons at 9 and 18 years of age, and found that twins had a lower systolic BP of 4.55 mmHg, compared to singleton children and adolescents. A recent Dutch study found that smaller twins weighing 1,036 g less than their singleton siblings had the same BP.[18] Their findings were based on 204 monozygotic (MZ) twins versus 71 singleton siblings and 271 dizygotic (DZ) twins versus 103 singleton siblings at 25 and 50 years of age.

A longitudinal study of 137 African Americans from birth through 28 years of age was conducted by Hulman et al.[19] No correlation was found between BW and BP. In addition, no hypertensives were found among adults with a BW <2,500 g. Adults with BW >3,800 g had a substantially higher percentage of hypertensives, compared to those with a BW of 2,500–3,200 g. They concluded that excessive growth rates and greater obesity starting in childhood, rather than lower BW, may result in a body size that exceeds organ functional capacity.

A study of 165,136 18-year-old men found a very small negative correlation (r=-0.03) between BW and BP.[20] However, much larger positive coefficients were found between BP and current body height (r=0.08) and weight (r=0.15). The researchers concluded that the relation of birth size to fetal growth and development problems and its importance to clinical and public health considerations is "...highly speculative and uncertain.[20]"

As mentioned, studies of the impact of BW on BP often adjust for current body size. In the preceding examples, three studies did not adjust for current body size.[12,15,19] One study[16] found a positive correlation between BW and BP, but this correlation became negative when the findings were corrected for current weight. Three other studies[16-18] found correcting for current body size had only a small impact on BP. Two other studies[13,14] found small positive relations between BW and BP without any adjustments, but greater current body size had a much larger impact.

Figure 1.
Increasing incidence of myocardial infarction with increasing BW: prospective study of 855 50-year-old men born in 1913 and tracked from 1963 to 1993. (Trend line based on data from Eriksson et al.[21])



Impact of Higher BW and Resulting Larger Body Size on Adult Health

The negative impact of BW and larger body size (including greater obesity) on adult health outcomes has been found by many researchers. The following summarizes some of these findings.

Eriksson et al.[21] tracked 855 50-year-old men for 30 years and found that total mortality was lowest for the 26–50 percentile of BW. In addition,the myocardial infarction rate increased progressively with each higher BW quartile (Figure 1).

A study[22] of 14,786 twins in Sweden evaluated their mortality in relation to lower BW (twins were 900 g lighter than singleton births). The twins averaged about 73 years. Death from ischemic heart disease (IHD) was found to be about the same for twin females as for the general population. However, twin males had a lower IHD risk ratio (0.85). Another twin study by Christensen et al.[23] tracked 8,495 twins born 1870–1900 through 1991.

Table 1. Comparison of Increasing Height and Decreasing Life Expectancy in Various Sample Populations

Population (Taller Versus Shorter)	Regression Slope of Reduced Life Span Versus Height Increase (year/cm)
VA medical center (males)	–0.47
Baseball player (males)	–0.35
U.S. presidents (males)	–0.35
Harvard athletes (males)	–0.70
Finnish cross country skiers versus basketball players (males)	–0.49
Ohio coroner's office (n=1,700 deceased men and women)	–0.53
U.S. basketball players (males)	–0.47
French (males)	–0.59
California white males versus females	–0.47
California Asian males versus females	–0.55
California Hispanic males versus females	–0.55
California Black males versus females	–0.63

Adapted from *Bulletin of WHO*, 1992;70:259-267.

Mortality of smaller BW twins was not significantly different from the general population; e.g., twin females aged 60–89 had 1.14 times higher mortality. However, for ages 30–69, larger BW female DZ twins had 1.77 times higher mortality than smaller MZ twins. Male MZ twins had a slightly lower mortality than the general population up to 50 years of age.

Dahlquist et al.[24] evaluated 892 cases of childhood type-1 diabetes against 2,291 control subjects. They found low BW (<2,500 g), short BL, and being first born were protective. In addition, being small for gestational age did not increase risk.

BL, Low-BMI Mothers, and Infant Mortality

The benefit of greater BL is also subject to question. For example, a study of >1.7 million subjects[25] found that perinatal mortality was more strongly related to BL than to BW or gestational age. In addition, mortality rates were lowest for a BL between 0 and 2 cm below average. The lowest mortality (0.6 death/1,000) occurred with a BL of 49 cm and a BW of 3,250–3,499 g for the period of 1992–1997. The perinatal mortality for the 3,749–4,990-g BW cohort was calculated to be ~1.5 deaths/1,000 or over twice the rate of the lower BW cohort.

In general, larger maternal size is correlated with high BW and lower perinatal mortality. However, optimum maternal body size is also in question considering the findings of Rantakallio et al.[26] Over 20,000 women consisting of two cohorts who were parturient in 1966 and 1985–1986 were studied. A BMI of 15–20 kg/m^2 was found to produce healthy children, compared to the usually defined BMI of 20–25 kg/m^2. Although small women produced more preterm, low BW, and small-for-gestational-age infants (who generally have higher mortality rates), the overall mortality of all children from the perinatal period to four years later was substantially lower for the 1985–1986 cohort of women with a BMI of only 15 kg/m^2 or a weight of 40 kg. Childhood mortality increased for mothers who had a BMI increase from 15- to 35 kg/m^2 or had a weight increase from 40- to 90 kg. For the earlier cohort (1966), mortality risk was lowest for a BMI of 20 kg/m^2 and increased up to 35 kg/m^2. Mortality risk also increased with a BMI under 20 kg/m^2 but was lower than for BMIs exceeding 28 kg/m^2. Mortality risk was flat from 40- to 90 kg for the 1966 cohort. Compared to the 1966 cohort, the large reduction in mortality for the 1985–1986 parturient cohort occurred concurrently with an 80% increase in women with a BMI below 20 kg/m^2.

Rantakallio et al.[26] also found that the impact of maternal height on childhood mortality was inconsistent. For the 1966 period, infants born to taller mothers had lower mortality, but for the 1985–1986 period, mortality was flat with increasing height.

An earlier study found that smaller Vietnamese-born mothers in Australia gave birth to lower BW infants, compared to larger Vietnamese mothers born in Australia.[27] However, perinatal mortality was 54% higher for the larger babies of Australian born mothers. They also found that interventions for labor or delivery were also higher for the larger babies.

Fetal Macrosomia

Large infants (≥4,000 g) represented 9.1% of deliveries in a study by Wollschlaeger et al.[28] This condition was tied to greater maternal nutrition and body size of the mothers, compared to the control group. Mothers of large infants weighed 6.1 kg more than the controls in early pregnancy. Fetal macrosomia was tied to higher frequency of operative deliveries, birth injuries, pre-eclampsia, and postpartum hemorrhages. Males had a higher risk of shoulder dystocia and birth injuries. They also found higher BW infants had higher insulin levels. Other studies have reported that macrosomia may be tied to neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, and other serious problems during the first hours of life.

The proportion of high-BW children is increasing in Nordic countries. Over 20% of newborn Swedes exceed 4,000 g and experience increased major perineal ruptures and brachial plexus damage.[29] Large BW also increases childhood and adulthood morbidity, including type-1 diabetes, eczema, breast cancer, and prostate cancer.

BW and Cancer

Childhood cancer is the second leading cause of death in children <15 years of age.[30] Several studies have found a correlation between childhood cancers and high BW (>4,000 g). Yeazel et al.[30] found an increased risk of acute lymphoblastic leukemia, Wilm's tumor, and neuroblastoma with increasing BW. While four studies showed no relation to BW, at least nine studies found an elevated risk for childhood leukemia with high BW.

Tibblin et al.[31] studied 366 50-year-old men and found that the highest quartile of BW had about a five-times-higher incidence of prostate cancer, compared to the lowest-BW men. Ekbom et al.[32] reported that higher adult prostate cancer mortality occurred in subjects who had higher PIs at birth.

A progressive increase in breast cancer with rising BW was found by Michels et al.[33] Infants weighing <2,500 g had half the risk of infants >4,000 g. Risk increased for each of five BW groupings. Based on a 51-year follow-up study of 2,221 women,[34] the risk of breast cancer for a BW ≥3.5 kg was 1.76 times that for a BW <3.5 kg. In addition, women who were heavy at birth and tall at seven years had a breast cancer risk four times greater than women of lower BW and height at seven years of age.

Barker et al.[35] studied 5,585 women and found the lowest ovarian cancer deaths among those with BW of 2,727–2,954 g. At 1 year of age, children >10.9 kg had a 4.4 times higher cancer rate, compared to the lightest weight children (<8.2 kg).

A comprehensive systematic review of over 300 cancer and height studies[36] found that an association exists between taller height and cancer with an increased risk of 20–60%. However, many studies have found that risks can exceed this range (e.g., 140% increased risk). In addition, Okasha[37] found that greater BW and childhood and adult tallness are positively correlated with cancer, and many large studies show a linear relation between height and cancer.

Rapid Childhood Growth and Health Problems

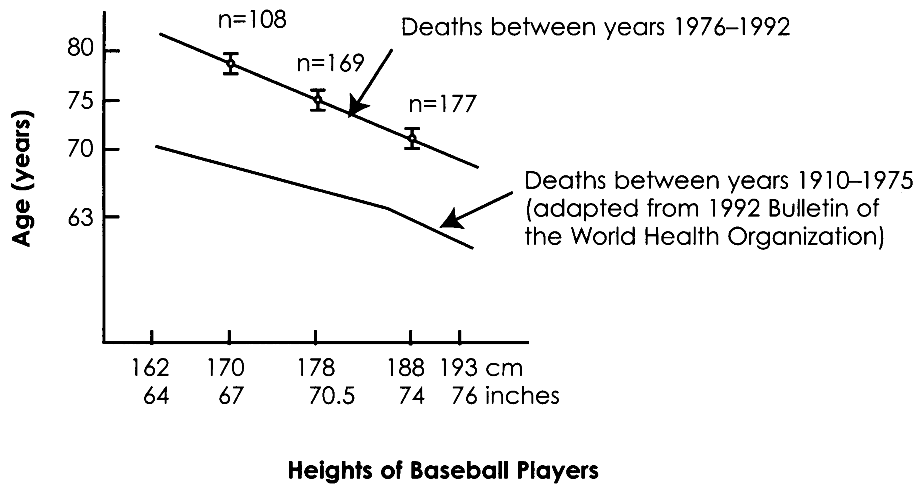
Huxley[9] reported that 13 out of 16 studies show rapid growth during childhood promotes higher BP. Rapid growth is also related to obesity and other diseases.[38,39]

Type-1 diabetes is occurring at increasingly younger ages in affluent countries. Bruining[38] found that children who became overweight in the first year of life and had a greater-than-normal increase in height during the next two years were more likely to become type-1 diabetics. The worldwide trend towards greater body size has been linked to increased insulin levels and type-1 diabetes.

Eriksson et al.[39] found that children with the greatest height change between ages 7 and 16 years had the highest risk for stroke in adulthood. The lowest height increase had half the risk. Social class and income were inversely related to stroke in adulthood. The lowest stroke rate was found for high-income males with BW of 3,001–3,500 g.

The Bogalusa Heart Study evaluated 105 children for height and obesity trends based on the age of adipose rebound (childhood age in which minimum BMI occurs and starts to increase again). The subjects were examined at 5, 6, 7, 8, and 19–23 years of age. Freedman et al.[40] found that early adipose rebound (AR) was tied to higher levels of

Figure 2. Reduction in Baseball-Player Lifespan With Increasing Height
(Used with permission of the *Journal of the Washington Academy of Sciences*, Washington, DC)



BMI in adulthood. Children that had an AR ≤5 years of age had a BMI 4–5 kg/m^2 greater in early adulthood versus children with an AR ≥7 years of age. The researchers concluded that greater childhood height and adiposity promoted early maturation and greater adult obesity. Other studies[41] found childhood height correlated with higher adult levels of BMI, triglycerides, and insulin. Higher BMI also correlates with lower HDL and higher levels of serum cholesterol and IGF-1.

In a study of 19,397 full-term children, Stettler et al.[42] found that rapid growth during the first four months of life was correlated with increased risk of overweight at 7 years of age. (It has also been shown that childhood overweight tracks into adulthood.[43,44]) The greater incidence of overweight due to faster growth occurred for all BWs. For example, the prevalence of overweight in the lowest-weight quintile with the fastest growth rate was four times greater than for the lowest growth rate. For the highest-BW quintile, the prevalence of overweight was three times greater for the highest growth rate than for the lowest.

Albanes[45] reported that high food intake during childhood promotes rapid growth and cancer; e.g., adult cancer incidence increases by 20% for each megajoule increase in total energy during childhood. Other studies found that men ≥183 cm had a 36% higher cancer rate than those ≤168 cm, and prepubertal children experienced 80% higher cancer mortality 50 years later with every 3–4-mm increment in leg length above average.

BW, Adult Height, Longevity, and Heart Disease

Studies have found BW and adult height are linearly related,[2,46] and a number of studies have tied lower CVD and lower mortality to greater stature.[47,48] However, many exceptions exist within and between populations.

In the developed world, the longest-living people are shorter than average. The Japanese, Hong Kong Chinese, Greeks, and Cypriots all have had exceptional longevity. Adult males average about 162–168 cm. In addition, a number of studies of deceased populations have found an inverse relation between height and longevity.[47-50] Figure 2 shows the height–longevity relation for more than 3,600 deceased baseball players.[49] Figure 3 shows the relation between shorter and taller 19th-century French men.[49] Table 1 compares the decline in longevity with a 1-cm increase in height for various populations.[47-50] Most recently, a Swedish study by Krakauer et al. found tall height was predictive of higher mortality (personal communication 12/7/2001).

In relation to heart disease, the relatively short Cretans were found to have 1/20 the CHD death rate, compared to northern Europe and the United States.[47] The Japanese and Chinese also have a much lower CHD mortality rate, compared to taller northern Europeans and Americans. Campbell and Chen found CHD and cancer mortality increased with increasing height in a large ongoing study in China.[47] In addition, the increase in CHD in China over the last 40 years has paralleled increasing height.

Other short people with low CHD include the Okinawans, Congo Pygmies, Navajo, Papua New Guineans, Eskimos, Solomon Islanders, and southern Europeans. In California, shorter ethnic groups have much lower CHD and all-cause mortality.[47-50] In addition, smaller peasants in Asia, Africa, and Central American rarely have CHD. We also found over 30 populations in which short people have had superior longevity.[47-50] Some are shown in Table 1.

Lindeberg et al.[51] studied the Kitavans (Papua New Guinea) and found no evidence of CHD or stroke. Subsequent follow-up through the year 2000 has confirmed these findings. These healthy people living according to their traditional diet and lifestyle average 162 cm for males and 150 cm for women. Although food is plentiful, the BMIs of the elderly are 19 for men and 17 for women. Interestingly, young Kitavan women average 46 kg—a weight considered a high risk by western researchers for low-BW infants and subsequent adult CVD.

The Cornell China Study found very low CHD mortality rates in the rural Chinese over a three-year period.[52] Males in Guizhou county had the lowest rates. No CHD deaths were found for males ≤64 years of age out of a population of 246,000. In Sichuan province, females ≤64 years had no CHD deaths out of a population of 181,000 women. Men averaged under 164 cm and 55 kg, and women under 154 cm and 49 kg.

Many studies have found that higher BW and linear growth are related to higher adult BMI or obesity.[2,17,43,44] A higher BMI is undesirable based on a recent 10-year follow-up study of 123,750 female nurses and male health professionals which found a BMI range of 18.5–21.9 had the lowest risk of common chronic diseases, including heart disease, hypertension, diabetes, and colon cancer.[53] They found that risk increased even in the upper half of the BMI range (22–24.9) normally considered healthful. A Chinese study by Hu et al.[54] found that there was no threshold BMI for CVD risk factors as illustrated by the linear increase in hypertension with BMI, shown in Figure 4.

Animal Studies, Body Size, and Longevity

Over the last 70 years, hundreds of animal studies have found that caloric restriction (CR) after weaning is the only known method for extending lifespan in a wide range of species.[50,55-57] Animals are substantially smaller due to CR without compromising morbidity or mortality, and large mice have shorter lifespans than normal size mice. Recently, Rollo conducted the first global analysis of 20th-century studies on mice and rats. Based on 796 populations, he found a strong negative correlation (-0.36, $p<0.00001$) between longevity and body size.[57] Some important findings by Bartke[56] and Rollo[57] that relate to body size are summarized next:

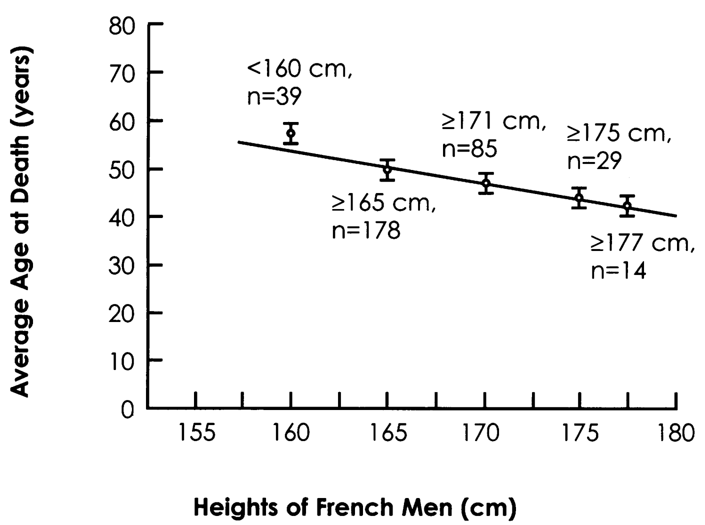
- Within the same species, smaller animals generally live longer than larger ones.
- Rapid juvenile growth leads to larger adult size and shorter longevity.
- Long-lived dwarf mice on ad-lib feeding live even longer on CR.
- The greater the degree of growth retardation, the greater the longevity.
- Maximum longevity declines with increasing mass at maturity.
- The difference in longevity between males and females is due to size dimorphism.

Over the last 12 years, three organizations have been conducting CR experiments with nonhuman primates with similar results, although it is still too early for a final conclusion.[47,50] However, the latest findings indicate that only 15% of the CR monkeys died thus far, compared to 24% of the ad-lib controls.[58] While these studies don't contradict the disadvantages of fetal growth retardation, it appears that slow growth with a low-calorie, nutritious diet may provide substantial health benefits for humans.[47]

BW and Intelligence

We have discussed the issue of whether low BW and the correlates of short stature and smaller brain weight are related to lower intelligence in a previous paper.[59] Many studies indicate that higher-BW and taller children and adults are more intelligent.[60] However, we found over 30 studies that do not

Figure 3. Height Versus Lifespan of 19th-Century French Men
(Used with permission of the *Journal of the Washington Academy of Sciences*, Washington, DC)



agree with this conclusion. In addition, most studies have found small differences of only a few IQ points. Women have smaller brains than men, but their intelligence is equal to that of men. In addition, Asians are shorter and have smaller brains but have demonstrated equal or greater academic and professional achievements in the United States, Japan, Hong Kong, Singapore, China, India, and South Korea.[61,62] Four reports showing no or little difference in adult IQ between small- and normal-sized babies are discussed next.

Posthuma et al.[63] evaluated the intelligence of twins against their singleton siblings. Based on 358 subjects, no difference in cognitive performance was found. The twins averaged about 1,000 g lighter at birth and were tracked to 38 years of age. Posthuma (personal communication 09/27/01), reported that the sample size was recently expanded by 300%, and subsequent analysis confirmed that no IQ difference existed between twins and singletons. The importance of this study is that SES and hereditary differences were minimized, compared to other studies.

Another study compared BW to intelligence scores at age 17 years.[64] Based on 13,434 full-term infants, a slightly lower IQ for children born small for gestational age was found, but this difference did not affect academic achievement. Also, low-BW babies were not at higher risk for low IQ (<85).

Hack[65] reviewed available literature on the long-term effects of intrauterine growth retardation (IUGR) on mental performance in late adolescence and adulthood. He reported on 15 studies that involved IQ assessment in adolescence and adulthood and found that no significant differences in IQ or behavior were evident for IUGR children when adjusted for SES. Hack also reported that prenatal exposure to famine in Holland during World War II had no effect on IQ; e.g., no clear relation between BW and intelligence was evident based on 125,000 males born in seven famine areas and 11 non-famine areas.

Perhaps the strongest position against a relation between brain size and intelligence was taken by Henneberg,[66] who stated that, "The relationship between brain size and intelligence, as measured by IQ tests or socioeconomic performance within present-day humans, is practically nonexistent.[66]" He noted that over the last 30,000 years, the human brain has declined in weight by 10%. Yet, phenomenal human achievements have paralleled this reduction in brain size.

Roots of the Obesity Epidemic

Elrick et al.[67] recently described the missing links and roots of the obesity epidemic as excess nutrition during childhood and adulthood, a dysfunctional food culture, lack of exercise, and overconcern with "normal" growth curves. Gillman[68] and Rush[69] pointed out that maternal energy and macronutrient intake have only a small impact on BW (except for extremes in intake). In addition, Gillman reported that interventions to increase BW are "...potentially harmful."[68] Also, a meta-analysis by Parsons et al.[70] found that higher BW was correlated to adult obesity.

Some years ago, Amador et al.[71] reported that the same factors that increase adiposity increase lean body mass and height. Another way of looking at this relationship is: a diet that increases height also increases lean body mass and adipose tissue. Martorell et al.[72] also observed that poor nutrition early in life is not tied to later obesity and the obesity epidemic. However, intrauterine overnutrition as indicated by high BW has a long-lasting impact on subsequent fatness; e.g., they found that adults with BW below 3,000 g were not prone to overweight, but those heavier than 3,499 g were at risk of severe overweight.

Parsons et al.[73] found that children who attained a greater percentage of their adult height by 7 years of age had greater than average BW and higher risk of obesity at 33 years of age. They also reported that the Amsterdam Growth and Health Study found a high percentage of calories from protein during childhood is related to adult obesity. In addition, faster growth during the first seven years of life promotes greater obesity in adulthood, according to Eriksson et al.[43]

As mentioned before, it is important to realize that relatively small differences in BW can result in substantial increases in overweight and obesity in adulthood. Amador[71] found a BW of >3,499 g correlated with obesity. Likewise, Sorensen et al.[74] found that normal-weight adults averaged a BW of 3,445 g, overweight adults averaged 3,548 g, and obese adults averaged 3,571 g. Thus, the difference between normal weight and obesity in adulthood was tied to a difference of only 126 g in BW.

The increase in obesity of today's population is not only due to excess food intake in childhood and adulthood but to larger body size of mothers. As discovered in other studies, Forsen et al.[75] found that the weights and heights of children are positively related to their mother's weights and BMIs. They also found that above-average increases in weight and height of children born to heavier mothers were independent of BW. Attempts to increase the size of low-BW infants may establish a pattern of overnutrition, which leads to childhood, adolescent, and adult obesity. Thus, efforts to correct for low BW and shorter height may be inadvertently promoting the obesity epidemic.

Impact of Genetic Engineering on BW and Body Size

The next few decades will complicate life further, because genetic engineering will allow the embryo to be modified for characteristics desired by the parents.[76] Stock reported that, "The question is no longer *whether* we will manipulate embryos, but when, where, and how."[77] He further stated that direct manipulation of the human embryo will be possible in 10 or 20 years. As long as tall stature continues to have strong favor in our society, parents will want their children to be taller than average. For example, based on their research, Martell and Biller[78] reported that the ideal height is 188 cm for males and rising as the average height increases. Genetic alterations for increased height will probably increase BW and future body weight and obesity. Such a trend has harmful ramifications for our health, environment, and economy. The ramifications of increasing height and body size were discussed in previous papers[49,59] and are not discussed here. However, we should not produce heavier and taller children through genetic engineering without a thorough evaluation of the ramifications of this practice.

DISCUSSION AND CONCLUSIONS

Disentangling the connections between BW and health throughout the life cycle is difficult due to the various confounders involved. Recently, Wilcox[79] presented evidence challenging the causal relation between BW and health outcomes. Rush[69] also stated that, "the simple relationship between maternal macronutrient status and perinatal survival....that is usually posited....is no longer defensible.[69]" In addition, high infant growth rates may be part of the obesity epidemic as previously discussed.[42] Of course, maternal, fetal, and infant nutrition is related to infant and future health, but adult factors seem to be the most important. For example, a 22-year follow-up study in Great Britain found that CVD incidence and mortality of 62- to 81-year-old males were predominantly related to factors in adult life.[80]

This paper has presented findings indicating that moderately lower BW as such is not harmful to

Figure 4. Increase in Hypertension Incidence With Increasing BMI
(Trend line based on data from Hu et al.[54])

childhood and adult health. However, neglect, malnutrition, maternal illness or smoking, and exposure to toxic substances is certainly harmful regardless of an infant's BW (e.g., low, normal, or high BW). In addition, a high-BW infant that has slower than normal growth may experience health benefits.[81]

While the findings on BW and intelligence are mixed, we believe that the findings presented in this paper provide substantial support for the thesis that BW and brain size are not related to intelligence when other factors are considered, such as SES, smoking, malnutrition, and explicit fetal brain damage. The presented findings are based on much larger populations than most studies which show that BW is positively correlated with intelligence. For example, Asians represent billions of people who are as intelligent as larger-brained caucasians. In addition, Hack's review of available studies found no difference in IQ for adolescents and young adults, and the Dutch study comparing low BW adults exposed to famine to nonfamine control groups showed no difference in IQ for a population of 125,000 subjects. Henneberg's findings that the human brain has decreased in size over the last 30,000 years also fails to support the importance of brain size in relation to intelligence in view of human achievements over the last 5,000 years.

It is certainly true that BP in adulthood is affected by many factors, including increasing weight, salt intake, stress, physical fitness, and the rate of accumulation of fatty deposits on blood vessel linings. Thus, small differences in BP due to low or high BW are not very important. However, the evidence is consistent that substantial increases in BP parallel increasing height, body weight, and BMI (even when it is considered within normal limits). Thus, BW independent of future body size appears to have little significance; e.g., Leon found only a small correlation between BW and BP of r=-0.03 for 165,000 adult males.[20]

In the past, many studies have linked BW to health outcomes after adjusting for current BMI or by comparing adult cohorts with similar BMIs. Since higher BW generally produces adults with greater height, weight, BMI, and BP, adjustment for current body size is misleading. Thus, adjustments should not be made for current height, weight, and BMI, since they are often related to BW and the rate of childhood growth.

Using current standards for weight gain can lead to overfeeding pregnant women resulting in increased BW and perinatal mortality.[69] In addition, overfeeding low BW children to attain catch-up growth provides confounding results based on current height and weight standards for particular ages.[81] This excess nutrition can lead to excessive BP and weight gain and potentially harmful adult health outcomes.[72,74]

When a new study confirms the growth retardation hypothesis, the researchers claim that debate is dead. However, before long a new study reopens the debate; e.g., last year, Stein et al.[82] reported that they found low BW had no relation to CVD risk factors in young adult females and only a weak relation for young adult men, unless they were overweight. They also reported that BP for adult men was independent of BW but increased with BW for females. Too many exceptions exist as to whether lower-than-normal BW is a root cause of poorer health in later years; e.g., low BW may simply be a covariant of other harmful consequences of intrauterine, genetic, preterm, and sociodemographic problems. In addition, it is clear that low and normal BW without fetal injury or health problems has long-term advantages with a lifelong healthful diet and low weight. Even if higher BW has initial advantages, the negative consequences of greater adult body size and obesity appear more important. As reported in this paper, ample evidence from Okinawa, Crete, South Africa, and other populations shows that low-calorie diets during childhood are consistent with low chronic disease in adulthood.[47,50,83,84]

Past emphasis on linear growth may have led to excessive nutrition to avoid stunting. Freedman et al.[85] recently observed that the secular increase in height may be rooted in overnutrition during infancy. Their view makes sense based on studies which show that rapid increases in height and weight during childhood are correlated with increased BP, diabetes, stroke, cancer, and obesity in adulthood.

Large adult body mass which correlates with higher BW, faster linear growth, and final height has also been found to reduce longevity in humans. A review recently published found a decline in longevity of 0.4 year/kg.[86] Some of the studies reviewed showed that higher crude weight in youth was correlated with reduced longevity. Since some of these studies were based on the weights of young athletes, their weights were relatively free of obesity.

Health professionals in the developed and developing world need to keep the following findings in mind when considering the optimum BW and growth rates for fetuses, infants, children and adolescents. However, it is important to note that while the findings are based on longitudinal and large sample studies, conflicting evidence exists for some of the items listed.

1. BW is strongly correlated with adult height, BMI, obesity, and BP.[17,44]

2. High BW and BL and rapid growth promote earlier puberty and early puberty is tied to increased breast cancer and obesity.[37,87]

3. Adult obesity increases with increasing BW or infant PI.[2,8,43]

4. BL has an independent effect on perinatal mortality, and minimum mortality occurs for BL 0–2 cm below average.[25]

5. Children who were heavier at birth and who experienced rapid growth in height were at higher risk for obesity at 33 years of age.[73]

6. Mother's body mass is + r with weight and height of children at all ages.[88] However, reduction in the rate of weight gain reduces subsequent CVD risk.[44]

7. Children exposed to famine conditions during midgestation had a lower mortality in adulthood (18–50 year), compared to those not exposed to famine at other stages of gestation.[89]

8. Accelerated growth results in increased adult insulin, BP, diabetes, CHD, and stroke.[39,44,75]

9. Height, weight, and BMI in childhood is + r with adult height, weight, and BMI at 24 years of age.[44]

10. Small mothers (15–20 kg/m^2) were found to have children with the lowest mortality from the perinatal period to 4 years of age.[26]

11. Overnutrition during infancy may explain the secular height increases of the 20th century. Also, children who experience adipose rebound ≤5 year versus ≥7 have a 4–5 point increase in BMI as adults. In addition, tall children are much more likely to have a BMI ≥30 and a skinfold sum of >90 percentile in adulthood.[40,85,90]

12. Promotion of increased height and weight in childhood may be harmful to adult health because the longest living people are often relatively short and light.[50,86]

While the optimum BW is difficult to define based on problems related to low and high BW, Gissler et al.[91] concluded that the lowest morbidity and mortality occurs at 3,500 g based on 60,000 infants tracked from birth to 7 years of age. Vanhala et al.[92] also found that a BW of 3,051–3,380 g for females and 3,300–3,590 g for males had one-fifth the incidence of metabolic syndrome in adulthood, compared to the highest BW adults (>3,730 g for females and >3,930 g for males.) Although a lower BW may not be the optimum for minimum morbidity and mortality during the perinatal period, the authors believe that the optimum combination would be a BW of 3,000–3,500 g, slow-to-moderate growth through adolescence, and moderate height and low body weight in adulthood. This would also provide a minimum neonatal and fairly low perinatal mortality and lower risk for adult obesity.[68,69,71,79,90]

Future advances in medical science may be able to minimize the negative health effects of increased BW and body size. However, the authors believe that this is a more difficult approach than preventing the creation of larger people in the first place.

The search for a BW which minimizes future health problems will continue. However, Lucas, Feutrell and Cole[11] have pointed out that implementation of this optimum BW will be a daunting project and postneonatal health problems will still persist. A sharp decline in infant mortality has occurred since 1900 along with reduced malnutrition and improved medical care and sanitation. Yet, many industrialized nations have reported an increase in premature births with U.S. whites seeing a 15.6% rise in the last 10 years.[93] In addition, the obesity epidemic has spread to most nations,[94] and we have a dismal CVD record compared to traditional societies unaffected by western diet and lifestyle. And we can't ignore the findings of two reviews by Parsons et al.[73] and Rush,[69] which found that higher BW was clearly related to adult obesity.[70] Increasing macrosomia, body weight, and calorie-rich nutrient-poor foods are the major problems, and their correction will require massive efforts from the medical profession and public health agencies. We believe that overemphasis on the importance of BW and growth charts in developed and developing countries distracts health professionals from the real health problems of overnutrition, overweight, trans fats, energy-rich fast food, physical inactivity, smoking, pollution, alcohol, and other drugs.

POSTNOTE

Since this paper was completed, two additional papers of importance were found. Huxley et al.[95] reevaluated a review published earlier[9] and concluded that BW has little relevance to BP in later life. The second paper, based on 2 million infants, found that BW declined over a 50-year period concurrent with reduction of stillbirth mortality from 21/1000 to 1.8/1000 for both males and females. Mortality rates were similar for BW from 2.5 to 4.5 kg.[96]

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